 See related commentary on pg 20

Objective Measures of Psoriasis Severity Predict Mortality: A Prospective Population-Based Cohort Study

Journal of Investigative Dermatology (2018) **138,** 228–230; doi:10.1016/j.jid.2017.07.841

TO THE EDITOR

A broad and growing body of literature suggests that psoriasis is associated with higher rates of major comorbidities, including mortality (Gelfand et al., 2007; Lee et al., 2017; Lindegard, 1989; Ogdie et al., 2014; Poikolainen et al., 1999; Salahadeen et al., 2015; Springate et al., 2017; Stern and Huibregtse, 2011; Svedbom et al., 2015). Most current literature does not adjust for major mortality risk factors such as obesity, and critically, to our knowledge there are no studies that evaluate how direct measures of psoriasis severity influence risk of death. Therefore, the objective of this study is to examine the risk of mortality in psoriasis patients compared with adults without psoriasis, stratified by simple physician-reported objective measures of disease severity while adjusting for major mortality risk factors routinely collected in clinical practice.

We conducted a prospective, population-based, cohort study using The Health Improvement Network, an electronic medical records database in the United Kingdom. Within The Health Improvement Network, we created a nested cohort of patients with psoriasis, who were followed prospectively as the Incident Heath Outcomes and Psoriasis Events (i.e., iHOPE) study, as previously described (Yeung et al., 2013). Physician survey was used to confirm the diagnosis of psoriasis and classify, a priori, the extent of disease based on standard categories used by the Centers for Disease Control and Prevention and the National Psoriasis Foundation for epidemiological studies of psoriasis. The outcome of interest was death. Data were collected prospectively from the date of physician survey until the individual died, transferred out of the practice, or reached the end of the data collection period. Covariates of interest included age, sex, body mass index (BMI), alcohol use, smoking, and medical comorbidities from the Charlson comorbidity index (CCI) (Charlson et al., 1987). The CCI classifies comorbid health conditions that may affect the risk of mortality and has been previously validated to be a strong predictor of 5-year mortality in UK medical records databases (Khan et al., 2010). Descriptive statistics were used to examine age, sex, and comorbidity distribution between psoriasis patients and control subjects. The mortality rate was calculated by dividing number of deaths over the total observation time, in 1,000 person-years. Cox proportional hazard regression models, adjusted for age, sex, and CCI, were created to determine the adjusted risk of death in psoriasis. Sensitivity analyses controlling for BMI, alcohol and tobacco use, and use of systemic therapy were performed. Statistical analysis was performed in STATA 14.2 (StataCorp, College Station, TX).

The analysis included 8,760 adults with psoriasis and 87,600 adults without psoriasis (Table 1). Psoriasis patients were more likely to be male and had a slightly higher BMI, but the average age was similar in both groups. Psoriasis patients had higher rates of chronic kidney disease, chronic obstructive pulmonary disease, diabetes, and history of myocardial infarction. Among the 8,760 patients with psoriasis there were 125 deaths, which resulted in a mortality rate of 3.35 deaths per 1,000 person-years (95% CI = 2.81–3.99). In 87,600 adults without psoriasis, there were 1,188 total deaths or 3.24 deaths per 1,000 person-years (95% CI = 3.06–3.43) (Table 2).

After stratification by physician-reported body surface area (BSA), there were 58, 38, and 29 deaths in the <3%, 3–10%, and >10% psoriasis groups, respectively (Table 2). In age and sex-adjusted models, only those with more than 10% BSA had a statistically significant increased risk of death (hazard ratio = 2.12, 95% confidence interval = 1.46–3.07). The risk of mortality in those with BSA greater than 10% remained elevated when adjusting for CCI (hazard ratio = 1.79, 95% confidence interval = 1.23–2.59). Results were robust to sensitivity analyses adjusting for BMI, alcohol and tobacco use, and use of systemic therapy (Table 2).

In this large, population-based, prospective study from the United Kingdom, patients with psoriasis BSA of more than 10% had 1.79 times increased risk of death, compared with age- and sex-matched adults without psoriasis after controlling for baseline predictors of mortality. Those with less than 10% BSA may be at a higher risk for clinically important comorbidities, but not with elevated mortality. Based on our results, we estimate there is 1 excess death in every 390 psoriasis patients with a BSA greater than 10% annually that cannot be explained by traditional risk factors identified in routine medical practice.

The findings are consistent with what can be inferred from the existing mortality literature. Previously published population-based studies found an increased risk of death in psoriasis patients compared with control subjects; however, this was using treatment received as a proxy for psoriasis severity (Gelfand et al., 2007; Ogdie et al., 2014;

Abbreviations: BSA, body surface area; BMI, body mass index; CCI, Charlson Comorbidity Index

Accepted manuscript published online 23 August 2017; corrected proof published online 3 November 2017

Table 1. Baseline characteristics of psoriasis patients and controls

Characteristics	Controls N = 87,600	All Psoriasis N = 8760	*P*-Value
Female, n (%)	46,352 (52.9)	4,330 (49.4)	<0.001
Age in years, mean (SD)	45.3 (11.1)	45.4 (11.1)	0.596
BMI, mean (SD)	27.1 (5.7)	27.9 (6.1)	<0.001
Alcohol use			<0.001
Never	8,659 (9.9)	733 (8.4)	
Current/former	68,739 (78.5)	7,076 (80.8)	
Missing	10,202 (11.7)	951 (10.7)	
Smoking			<0.001
Never	42,609 (48.6)	3,209 (36.6)	
Current/former	43,616 (49.8)	5,474 (62.5)	
Missing	1,375 (1.6)	77 (0.88)	
Medical comorbidities, n (%)			
Cerebrovascular disease	969 (1.1)	108 (1.2)	0.282
Chronic kidney disease	1,889 (2.1)	233 (2.66)	0.002
Congestive heart failure	251 (0.3)	32 (0.4)	0.194
Chronic obstructive pulmonary disease	15,434 (17.6)	1,622 (18.5)	0.036
Dementia	39 (0.04)	6 (0.07)	0.322
Diabetes	3,831 (4.4)	461 (5.3)	<0.001
Hemiplegia	114 (0.2)	8 (0.1)	0.100
HIV	11 (0.01)	1 (0.01)	0.927
History of myocardial infarction	908 (1.0)	129 (1.5)	<0.001
Peripheral vascular disease	528 (0.6)	75 (0.9)	0.004
Liver disease	695 (0.8)	93 (1.06)	0.008
Malignancy	2,188 (2.5)	185 (2.1)	0.026
Charlson Comorbidity Index, n (%)			<0.001
0	63,201 (72.0)	6,097 (69.6)	
1–2	21,728 (24.8)	2,310 (26.4)	
3–4	2,316 (2.6)	291 (3.3)	
>5	454 (0.5)	62 (0.7)	

Abbreviations: BMI, body mass index; SD, standard deviation.

Salahadeen et al., 2015; Springate et al., 2017). In our psoriasis patients, only 21% of those with BSA of greater than 10% had a history of treatment with systemic therapy (phototherapy, oral systemic medication, or biologic), showing the need to use objective measures of disease severity to more fully capture patient experience. One previous study has examined mortality risk, using physician-reported objective measures of psoriasis severity. The PUVA Follow-Up Study prospectively followed 1,376 adults with severe psoriasis enrolled in a clinical trial for treatment with psoralens and ultraviolet-A (PUVA) (Stern et al., 1984). Our results confirm what was shown in the PUVA Follow-Up Study: a one-time measurement of psoriasis severity is a powerful predictor of future mortality (Stern and Huibregtse, 2011).

In summary, patients with psoriasis affecting more than 10%of BSA are at an increased risk of death compared with the general population, even after controlling for standard mortality risk factors. Our findings support the existing literature showing that patients with severe psoriasis have an increased risk of death and show that a one-time, simple clinical assessment can be predictive of future mortality.

Table 2. Hazard ratio of morality based on physician-reported psoriasis BSA

	Controls n = 87,600	<3% BSA n = 4,539	3–10% BSA n = 3,133	>10% BSA n = 1,088
Number of deaths	1,188	58	38	29
Average follow-up time, years (SD)	4.17 (1.64)	4.25 (1.56)	4.31 (1.50)	4.16 (1.53)
Mortality rate, per 1,000 person-years (95% CI)	3.24 (3.06–3.43)	3.00 (2.32–3.88)	2.81 (2.04–3.86)	6.39 (4.45–9.21)
Unadjusted HR	REF	0.92 (0.71–1.20)	0.87 (0.63–1.20)	2.00 (1.38–2.89)
Adjusted for age and sex	REF	0.89 (0.70–1.17)	0.87 (0.63–1.20)	2.12 (1.46–3.07)
Adjusted for age, sex, and CCI	REF	0.87 (0.67–1.13)	0.79 (0.57–1.09)	1.79 (1.23–2.59)
Attributable risk[1]	N/A	N/A	N/A	2.56 per 1,000 person-years
Sensitivity analyses				
Adjusted for BMI	REF	0.90 (0.69–1.18)	0.77 (0.54–1.08)	1.81 (1.23–2.68)
Adjusted for smoking and alcohol use	REF	0.80 (0.61–1.06)	0.70 (0.49–0.99)	1.76 (1.21–2.57)
Adjusted for cardiovascular risk factors[2]	REF	0.82 (0.63–1.08)	0.76 (0.55–1.06)	1.87 (1.29–2.70)
Excluding those who received any systemic therapy (UV, oral systemic, or biologic)				
		n = 4,478	n = 2,944	n = 856
Fully adjusted[1]		0.89 (0.68–1.15)	0.78 (0.55–1.09)	1.68 (1.08–2.61)
Excluding those who received oral systemic or biologic therapy				
		n = 4,509	n = 3,062	n = 988
Fully adjusted[1]		0.88 (0.68–1.15)	0.78 (0.56–1.08)	1.87 (1.26–2.75)

Abbreviations: BSA, body surface area; CI, confidence interval; CCI, Charlson Comorbidity Index; HR, hazard ratio; N/A, not applicable; REF, reference; SD, standard deviation.

[1]Adjusted for age, sex, and CCI.

[2]Adjusted for age, sex, smoking, diabetes, history of myocardial infarction, and history of stroke.

Based on these results, psoriasis patients identified in the clinic with BSA of greater than 10% should be targeted for preventative health interventions. Additionally, future research is needed to better elucidate the specific causes of mortality in patients with extensive psoriasis and determine the effects of psoriasis treatment on mortality risk.

ORCID

Megan H Noe: http://orcid.org/0000-0001-8481-4711

CONFLICT OF INTEREST

In the previous 12 months, JMG served as a consultant for Coherus (DSMB), Dermira, Janssen Biologics, Merck (DSMB), Novartis Corp., Regeneron, Dr Reddy's labs, Sanofi and Pfizer Inc., receiving honoraria; receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Janssen, Novartis Corp., Regeneron, Sanofi, Celgene, and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly and Abbvie. JMG is a co-patent holder of resiquimod for treatment of cutaneous T-cell lymphoma. MHN, DBS, and MTW state no conflict of interest.

***Megan H. Noe*[1,*], *Daniel B. Shin*[1], *Marilyn T. Wan*[1] *and Joel M. Gelfand*[1,2]**

[1]*Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania, USA; and* [2]*Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania, USA*

[*]*Corresponding author e-mail: megan.noe@uphs.upenn.edu*

REFERENCES

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373–83.

Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol 2007;143:1493–9.

Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. BMC Fam Pract 2010;11:1.

Lee MS, Yeh YC, Chang YT, Lai MS. All-cause and cause-specific mortality in patients with psoriasis in Taiwan: a nationwide population-based study. J Invest Dermatol 2017;137:1468–73.

Lindegard B. Mortality and causes of death among psoriatics. Dermatologica 1989;179:91–2.

Ogdie A, Haynes K, Troxel AB, Love TJ, Hennessy S, Choi H, et al. Risk of mortality in patients with psoriatic arthritis, rheumatoid arthritis and psoriasis: a longitudinal cohort study. Ann Rheum Dis 2014;73:149–53.

Poikolainen K, Karvonen J, Pukkala E. Excess mortality related to alcohol and smoking among hospital-treated patients with psoriasis. Arch Dermatol 1999;135:1490–3.

Salahadeen E, Torp-Pedersen C, Gislason G, Hansen PR, Ahlehoff O. Nationwide population-based study of cause-specific death rates in patients with psoriasis. J Eur Acad Dermatol Venereol 2015;29:1002–5.

Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CE, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. Br J Dermatol 2017;176:650–8.

Stern RS, Huibregtse A. Very severe psoriasis is associated with increased noncardiovascular mortality but not with increased cardiovascular risk. J Invest Dermatol 2011;131:1159–66.

Stern RS, Laird N, Melski J, Parrish JA, Fitzpatrick TB, Bleich HL. Cutaneous squamous-cell carcinoma in patients treated with PUVA. New Engl J Med 1984;310:1156–61.

Svedbom A, Dalen J, Mamolo C, Cappelleri JC, Mallbris L, Petersson IF, et al. Increased cause-specific mortality in patients with mild and severe psoriasis: a population-based Swedish register study. Acto Derm Venereol 2015;95:809–15.

Yeung H, Takeshita J, Mehta NN, Kimmel SE, Ogdie A, Margolis DJ, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. JAMA Dermatol 2013;149:1173–9.

A Missense Mutation within the Helix Termination Motif of *KRT25* Causes Autosomal Dominant Woolly Hair/Hypotrichosis

Journal of Investigative Dermatology (2018) **138,** 230–233; doi:10.1016/j.jid.2017.08.035

TO THE EDITOR

Woolly hair (WH)/hypotrichosis is an unusual condition characterized by sparse and tightly curled hair (Ramot and Zlotogorski, 2015a). WH may be isolated or be accompanied by additional complications including palmoplantar keratoderma, hypotrichosis, epidermal naevus, and cardiomyopathy (Ramot et al., 2014; Veraitch et al., 2016). Isolated WH can manifest with autosomal dominant (AD) or autosomal recessive trait of inheritance (Shimomura, 2016).

Keratins are scaffolding proteins that form a network of intermediate filaments (IFs). Heterodimerization between type I and II keratin to form keratin IFs is the basic building block for hair structure (Ramot and Zlotogorski, 2015b). The phenotypic heterogeneity caused by different keratin genes also depends on their location within different hair structures, including the cortex of the hair shaft, the cuticle, and the inner root sheath (Naeem et al., 2006).

Variants in keratins K71 and K74 were described in ADWH pedigrees, and polymorphisms in *KRT75* were implicated in the pathogenesis of pseudofolliculitis barbae (Fujimoto et al., 2012; Wasif et al., 2011; Winter et al., 2004). Recently, biallelic variants within *KRT25* were also related to autosomal recessive WH/hypotrichosis pedigrees (Ansar et al., 2015; Zernov et al., 2016).

Here, we describe a monoallelic pathogenic variant in a Chinese ADWH/hypotrichosis family, five-

Abbreviations: AD, autosomal dominant; IF, intermediate filament; WH, woolly hair

Accepted manuscript published online 9 September 2017